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First Named Inventor:	Arnold Neracher		
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Title:	Injection Device with Re-Usable Pressure Generating Means	Group Art Unit:	3751

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Francis Cole
(Signature)

Dear Sir:

Pursuant to 35 U.S.C. §119, to perfect the claim for foreign priority benefits in the above-identified patent application, enclosed for filing is a certified copy of European Application No. 00128096.5, as filed December 21, 2000, including specification and drawings.

Respectfully submitted,

DORSEY & WHITNEY LLP
Customer Number 25763

Date: November 11, 2005

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Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

00128096.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

Anmeldung Nr:
Application no.: 00128096.5
Demande no:

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Anmelder/Applicant(s)/Demandeur(s):

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Injection device with re-usable pressure generating means

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

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Internationale Patentklassifikation/International Patent Classification/ Classification internationale des brevets:

A61M5/30

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

Injection Device with Re-Usable Pressure Generating Means

Background of the Invention

The present invention relates to a device with reusable pressure generating means for injecting liquids, in particular for intracutaneous or subcutaneous injection of medicaments or other pharmaceutical compositions, such as vaccines.

Manually operated syringes with needles are the most common form of hypodermic injection devices. They have the advantage of being reliable and low cost. The disadvantages are, inter alia, the risk of transmitting diseases by re-use of the syringe, and the pain felt by the patient.

In view of these disadvantages, there have been many attempts to provide needleless hypodermic injection devices in which a liquid to be injected is propelled at high speed by a pressure generator, thereby piercing the skin of a human or animal patient. Such devices are, for example, described in patent publications US 3,537,212, US 2,687,725, US 4,596,556, US 4,722,728, US 4,874,367, US 4,966,581, US 5,501,666 and WO 98/41250. In order to ensure sterility and avoid contamination of medicaments to be injected, certain conventional devices as described in patents US 4,874,367 and US 4,966,581 comprise re-usable pressure generating mechanisms receiving disposable cartridges containing the liquid to be injected. The devices described in these patents are very complex and made of a large number of pieces. They are also bulky, costly and limited in their performance, particularly as concerns the injection pressure and jet diameter which are in the order of 70 bars or less and 100 to 330 µm, respectively, although initial peak pressure may attain around 300 bars. Insufficient pressure and a large diameter jet increases pain and the

risk that only a portion of the medicament is injected, especially with respect to patients having a resistant skin. The effectiveness of injection is important, particularly with patients such as diabetics who administer injections daily.

Considering the abovementioned disadvantages, an object of the present invention is to provide a hypodermic injection device that is sterile, effective and reliable. It is advantageous to provide a hypodermic injection device that is compact and cost effective. It is advantageous to provide an injection device that is safe to operate. It is advantageous to provide an injection device that eliminates the risk of disease transmission by re-use. It is advantageous to provide an injection device that is painless to use.

Summary of the invention

Objects of the invention have been achieved by providing the injection device according to claim 1.

Disclosed herein is an injection device having a propulsion system comprising a container, a re-usable pressure generating mechanism and a source of potential energy for propelling a fluid with sufficient pressure through an orifice to create a jet enabling sub-cutaneous delivery of the fluid, the source of potential energy primarily being in the form of a compressible substance that is put under pressure within the container by the pressure generating mechanism, whereby said potential energy is compression energy of said substance, wherein said compressible substance is a liquid, solid or other non-gaseous substance, as defined at ambient temperature and pressure.

The compressible substance may, for example, be a soft matter or other visco-elastic substance, such as a substance belonging to the family of polysiloxanes, which is not expensive and has a large elastic compression

range. Certain polysiloxanes may be compressed up to 2000 bars with a 15% volume reduction. Polysiloxanes comprise a volumetric compressibility (dV/V) which is in the range of two to four times greater than the volumetric compressibility of water.

In view of the very high pressure and small orifice diameter, it is possible to produce a very fine liquid jet of supersonic speed. Moreover, the injection time may be spread over a few seconds in view of the small jet diameter (e.g. 30-60 µm) thereby reducing or eliminating pain by giving more time for the medicament to diffuse in the surrounding tissue.

The provision of a compressed liquid or solid as a source of potential energy for propelling a liquid to be injected is very advantageous over prior art systems using mechanical energy sources such as springs, or compressed gas. The use of springs, for example, requires large dimensions to obtain the required propulsion energy to ensure that a patient's skin is pierced, and even then the liquid jet diameter is typically in the range of 200 µm in order to ensure sufficient speed of the jet. Prior systems using compressed gas, as defined at ambient temperature and pressure, are limited by the maximum pressure of the gas until a change of state to the liquid form, which defines the maximum pressure of the propulsion system. For example, carbon dioxide liquefies at approximately 70 bars and nitrogen protoxide at 75 bars, these gases being the most frequently considered for use in conventional propulsion systems. The large volume change of a compressed gas is also a safety concern, since in the event of rupture of the gas container, loose particles of the device are driven by the large expansion of gas liberated from the container.

Preferred compressible substances used in the invention, such as polysiloxane oils or gels, or vulcanised silicon rubber, which may be compressed for example to 2000 bars to obtain up to 15% volume reduction, do not cause an

explosion in the event of rupture. Furthermore, a liquid or solid compressible substance can be compressed in a container at much higher pressure since there is no change of state and the substance escapes less easily through the sealing joints than gaseous substances. Vulcanized silicon rubber or high molecular weight polysiloxane oils, for example, which are very viscous, are much easier to contain without leakage through seals compared to gas and even liquids with low viscosity such as water. While polysiloxane oils or gels are preferred substances in view of the combination of high viscosity, relatively high compressibility and low cost, numerous other substances with compressibility greater than water and preferably greater than double the compressibility of water could be implemented in certain embodiments of the invention. Examples of other compressible substances that may be implemented in the present invention are cork, polyurethane and butyl polymers. These substances have volumetric compressibility ratios (dV/V) in the range 1,2 to 2 times that of water.

The high energy density that may be stored in compressible substances according to this invention enables the hypodermic injection device to be compact and low cost.

Disposable cartridges or ampoules containing the liquid to be injected are mounted in the container by the user. This enables the ampoules to be manufactured, stored and used with the required sterility and accuracy of dosage. This also enables flexibility in the packaging and dosage of the liquid to be injected which can be determined by the volume in the ampoule.

The single use ampoule may further contain the compressible substance for assembly in the container, or the compressible substance could be provided in the container and re-used.

In some embodiments, the compressible substance may be put under pressure in a rear chamber of the container separated from a front chamber by a wall provided with a valve to actuate the device. When the valve is opened, the compressible substance flows into the front chamber and drives a piston that propels the liquid to be injected.

In other embodiments, both the compressible substance and the liquid to be injected are put under pressure in the container, the pressure being maintained by blocking the nozzle orifice with a removable plug.

In view of the high pressures that may be attained by the present invention, and therefore the high speed of the liquid jet produced, the jet may pierce the skin of a patient without the need for a needle in an effective, reliable and painless manner.

In the embodiments where a plug blocks the nozzle orifice, the plug may be of a material that may be decomposed by external means such as heat or ultrasound, for example a wax or paraffin plug that may be removed by locally heating the injection device. The plug may also be a mechanical member such as steel wire retractable from the orifice. The floating piston or deformable wall moves once the orifice is unblocked due to the drop in pressure in the capsule portion comprising the liquid to be injected.

In another embodiment, the portion of the single-use capsule containing the liquid to be injected is surrounded by a deformable wall arranged inside a portion of the capsule containing the compressible substance, and the retaining means comprise a plug closing the orifice of the nozzle portion. Once the retaining means are removed, the deformable wall of the container portion containing the liquid to be injected is crushed under the pressure of the compressible substance.

The container may be made of metal, for example made of stainless steel, which may be provided with a precious metal layer on its inside surface (for example gold, platinum, palladium) or with a polymer such as Teflon. The inside layer facilitates sliding of the piston and improves sealing. It should be noted that polysiloxane oils are very advantageous with respect to a gas, on the one hand, due to their viscosity which may be very high depending on the molecular weight of the oil, thereby reducing the demands on sealing, and on the other hand, a large portion of the stored compression energy may be transformed into work.

The nozzle portion may comprise a separate member mounted in or to the capsule container, or may be integrally formed with the wall of the capsule container.

The orifice of the nozzle portion may have a diameter in the order of 10 to 80 microns, at least over a defined length, such that the liquid jet remains coherent for a few millimetres after exiting the nozzle. If the displacement of the piston between the beginning and end of the injection corresponds to a variation in volume of the compressible substance of 7.5 %, this corresponds to a pressure variation of 1000 bars for monomer hexamethylsiloxane. A pressure of this order combined with a very fine nozzle orifice enables the production of a supersonic jet for liquid injections through skin in an extremely reliable and painless manner. Moreover, the supersonic shock wave causes degradation of the jet in droplets a few millimetres from the nozzle, thereby increasing the safety of the device. The jet could of course also be produced at subsonic speeds depending on the injection needs and requirements.

The compressible substance may be compressed by displacing a piston in the container, thereby reducing the volume occupied by the compressible

substance. The piston of the pressure generating mechanism may be displaced by a threaded member with a fine pitch engaging in a complementary thread at a rear end of the container portion.

Further objects and advantageous aspects of the invention will be apparent from the following description, claims and accompanying drawings.

Brief Description of the Drawings

Fig. 1 is a longitudinal section of a re-usable propulsion unit of an injection device according to this invention, for use with single-use capsules;

Fig. 2 is a longitudinal section of a capsule for assembly to the propulsion unit of Fig. 1;

Fig. 3 is a longitudinal section of a second embodiment of an injection device according to this invention, with a single-use capsule containing the compressible substance and the liquid to be injected mountable in a container of the propulsion unit;

Fig. 4 is a longitudinal section of the single-use capsule of the embodiment of Fig. 3;

Fig. 5 is a longitudinal section of the container and pressure generating mechanism of the propulsion unit of the embodiment of Fig. 3;

Fig. 6 is a longitudinal section of a variant of the embodiment of Fig. 3, in which the compressible substance is permanently mounted in the propulsion unit rather than to the single-use capsule.

Detailed Description of the Invention

Referring to Figures 1 and 2, an injection device comprises a propulsion system 1 and a disposable capsule 3 mountable thereto, for the administration of a liquid 2 contained in the capsule under the skin of a human or animal patient.

The propulsion system comprises a container 4, a pressure transmitting member in the form of a piston 5, a pressure retaining means 6, a pressure generating means 8, and a compressible substance 7. The compressible substance 7 under pressure is the principal source of potential energy for propelling the liquid to be injected.

The compressible substance may advantageously comprise a polysiloxane oil which has the ability to store a large amount of potential energy through elastic molecular compression, for example up to 100 times more energy than a conventional metal spring occupying the same volume. The molecules of polysiloxanes behave as three-dimensional springs, and the stored energy is equal to the sum of the molecular cohesion energy of about $4 \cdot 10^{-21}$ joules per molecule which corresponds to the thermal energy K_BT at 20° C, where K_B is Boltzmans constant, and T is temperature in Kelvin. The elastic property of polysiloxanes is particularly advantageous to the present invention since it allows the injection device to be compact, cost-effective, and comprise few components. Depending on the molecular weight, polysiloxanes typically have volumetric compressibility values (dV/V at a given pressure) three to four times greater that the volumetric compressibility of water. While polysiloxanes are a preferred soft matter for use in the present invention, other soft matter substances may also be used. The properties of soft matter are known and described, for example, in the reference "Review of Modern Physics", Nobel Lecture in Physics, vol. 64, p. 645.

resistant to high and low temperature and which are low-cost. They are neither toxic nor dangerous from the physiological point of view and may be used in dermatological and cosmetic applications. Polysiloxane oils have a low viscosity variation as a function of pressure which advantageously facilitates fluid exchange, but they have a high surface tension such that they are non-miscible with water solutions. Polysiloxane oils also have lubricating properties between metals and polymers and rubber, which advantageously facilitates sliding between mobile members.

The family of polysiloxane oils comprises, inter alia, the following substances:

- polymethylhydrogensiloxane
- polydimethylsiloxane
- polytrimethylsiloxane
- hexamethylcyclotrisiloxane
- decamethyltetrasiloxane
- hexamethyldisiloxane (H 7310 - Witheco)
- octamethyltrisiloxan (O 9816 - Witheco).

An advantageous property of polysiloxane oils is the reduction of viscosity with shear velocity which enables rapid flow of such oils through small orifices. Polysiloxane oils may have viscosities ranging from 0.6 to 10^7 centistokes depending on molecular weight. This property enables the oil to be chosen according to the requirements of the embodiment, in particular embodiments that require flow of the compressible substance through passages of small cross sections, as is the case for the embodiment shown in Fig. 1. The other embodiments may be provided with a compressible substance in the form of an elastic solid, such as vulcanised silicon rubber, for example of the type SilGel®

6/2 manufactured by Wacker-Chemie, having volumetric compressibility only about 25% lower than low viscosity polysiloxanes.

As an example, monomer hexamethylsiloxane $(CH_3)_6$ SiO may be elastically compressed under a pressure of approximately 2000 bars with a volume reduction of about 15%. If the volume of the liquid to be injected is 0.1 ml, and the minimum pressure at the end of injection is chosen to be 1000 bars, the non-compressed volume of polysiloxane is 1.3 ml. The device according to the invention is not only extremely compact, but enables the injection of liquid at pressures well above those available in conventional systems, which makes possible the production of a very fine jet that can surpass supersonic speed. Very reliable and safe hypodermic injection can thus be effected with the present invention.

For example, at 1000 bars pressure, the liquid to be injected can be propelled through nozzle orifices having diameters around 30-60 µm with sufficient speed to pierce a patients skin, and whereby injection time is slow enough to enable the injected liquid to diffuse in the surrounding tissue thus reducing injection pain. In conventional devices, the nozzle orifice must have a much larger diameter in view of the lower injection pressure, with the consequence that injection time is reduced and the injected liquid collects locally in the patient's tissue thus causing pain.

Moreover, the injection device according to the invention comprises very few parts which leads to low-cost production, in addition to simple and reliable use.

The pressure generating means comprises a piston closing a rear end of the container 4. A piston 10 closes a front end of the container portion 4. A separating wall 11, forming part of the pressure retaining means 6, is provided inside the container portion 4 between the rear piston 9 and front piston 10. A

large volume chamber 12 is formed between separating wall 11 and the rear piston, and a small volume chamber 13 is formed between the separating wall and the front piston. The separating wall is provided with a return valve 14 to allow compressible substance 7 from the front chamber to flow into the rear chamber, whereby flow in the opposite direction is prevented. An actuation valve 15 is provided to allow the compressible substance to flow from the rear chamber 12 to the front chamber 13 upon actuation of the valve, for example when the user presses a button 16 thereof.

The front end of the container is provided with a threaded portion 17 for releasably mounting a capsule 3 containing the liquid to be injected, the capsule being provided with a complementary threaded portion 18. Other releasable fixing means could however be provided, such as a bayonet type connection or releasable spring latches. A rear end of the capsule is sealingly closed by a piston 19 that is driven by the propulsion system piston 10 on actuation of the device thereby propulsing the liquid 2 through the nozzle orifice 20. The capsule piston 19 may be provided at its front end with a cone shaped elastic member 21 in order to ensure that substantially all the liquid to be injected is propelled out of the capsule.

The pressure generating mechanism 8 is mounted to the rear end of a container and comprises a grip portion 22 and a ram portion 23 in the form of a threaded bolt engaging a complementary threaded portion 24 of the container portion. As the mechanism 8 is screwed and the ram portion 23 is threaded into the container, the piston 9 is displaced and compresses the compressible substance 7. The amount of turns applied to the grip 22 determines the pressure of the compressible substance 7 which can thus be adjusted according to the application. To actuate the device, the user opens the actuation valve 15 by depressing the button 16 such that the compressible substance in the rear chamber 12 flows to the front chamber 13 and drives the

piston 10 which drives the capsule piston 19. After use, the capsule 3 is removed from the propulsion unit and the pressure generating element 8 is unwound, thereby aspirating the compressible substance 7 through the return valve 14 back into the rear chamber 12. A new capsule 3 may then be fitted into the front end of the container. It is advantageous in this embodiment to have a compressible substance of low viscosity, such as a low molecular weight polysiloxane, such that the flow resistance through the valves 15 respectively 14 is low.

In view of the short time between pressurising the compressible substance and injection, the sealing requirements are not particularly stringent compared to single-use propulsion units.

Referring to figures 3 and 4, another embodiment of an injection device is shown with a pressure generating mechanism 8 which may be similar to the one described in relation to figure 1, mounted to a reusable container 4 for receiving a capsule 3' comprising the liquid to be injected 2 in a flexible membrane 25 surrounded (at least partially) by the compressible substance 7 in a membrane 26. If the compressible substance is silicon rubber or other compressible solid rather than a liquid polysiloxane, the membrane 26 is not necessary. The capsule further comprises a nozzle portion 27 with an outlet orifice blocked by a plug in the form of a high tensile strength wire 28. The wire extends rearwardly through the membrane 25 into a long tail portion 29. The tail portion is received in a central passage 30 in the pressure generating mechanism extending through to the rear end 31 thereof such that the end 32 of the tail portion is accessible. The tail portion 29 may for example be made of plastic surrounding or encapsulating the wire 28. As the wire is very fine, for example around 50 µm diameter, the frictional force retaining it is quite low and very easily overcome by a user pulling on the end 32 to actuate the device by

liberating the nozzle orifice when the compressible substance is under operational pressure.

The container portion 4 can be made in two separable sections (not represented), or have a removable front end cap (similar to the embodiment of Fig. 6) in order to mount the capsule 3' therein. To apply pressure, the pressure generating mechanism is screwed inwardly after assembly of a new capsule.

Referring to figure 6, a variant of the embodiment of figure 3 is shown, in which the compressible substance 7 is mounted and remains in the container portion 4" whereas the single-use capsule 3" is removably inserted in the front end of the device which is provided with a removable cap 33 that is screwed or assembled by other means to the container.

The capsule 3" is provided with a wire 28 plugging the orifice of the nozzle portion 27 and extends in a tail portion 29 beyond a rear end 31 of the injection device in a similar manner to the embodiment of figure 3.

The capsule or ampoule membrane 25' is made, for example, of a plastic material, coated as appropriate for the pharmaceutical products contained therein. The nozzle portion 27 may be provided with a metal nozzle tip embedded in a plastic body, the tip being provided with an outlet orifice formed by a ductile insert crimped around the wire plug. The nozzle orifice may also be formed by overmoulding the nozzle portion 27 over the plug portion of the wire 28. The nozzle orifice may have a diameter as small as 5 to 100 microns, but is for most applications preferably in the range of 20 to 50 microns. The nozzle orifice extends over a length which is preferably between about two to five times the diameter of the orifice. The ratio between the orifice length and the diameter enables the production of a liquid jet that remains coherent over a distance sufficient to ensure reliable hypodermic injection, but which

destabilizes after a few millimetres, thereby making the jet harmless. In other words, the ratio between the length and diameter of the orifice enables the coherence of the jet to be regulated, such that it is sufficiently coherent for effective and reliable hypodermic injection without being too coherent for safety reasons.

Claims

1. An injection device having a propulsion system comprising a container, a re-usable pressure generating mechanism and a source of potential energy for propelling a fluid with sufficient pressure through an orifice to create a jet enabling subcutaneous or intracutaneous delivery of the fluid, the source of potential energy primarily in the form of a compressible substance that is put under pressure within the container by the pressure generating mechanism, whereby said potential energy is substantially compression energy of said substance, wherein said substance is a liquid, solid, or other non-gaseous substance as defined at ambient temperature and pressure.

2. Injection device according to claim 1, wherein the compressible substance has a volumetric compressibility (dV/V) at said pressure within the container greater than 1.2 times the volumetric compressibility of water.

3. Injection device according to any one of the preceding claims, wherein the compressible substance is a visco-elastic liquid or soft matter.

4. Injection device according to the preceding claim, wherein the compressible substance belongs to the family of polysiloxanes.

5. Injection device according to claim 1 or 2, wherein the compressible substance is an elastic solid.

6. Injection device according to the preceding claim, wherein the solid is vulcanised silicon rubber.

7. Injection device according to claim 1, wherein the volume of compressible substance is reduced by displacing a piston of the pressure generating mechanism.

8. Injection device according to any one of the preceding claims 1-4 and 7, further comprising a separating wall in the container enclosing the compressible substance in a rear chamber of the container, the separating wall comprising a valve that can be opened to enable the compressible substance to flow into a front chamber and transmit pressure to said fluid to be injected.

9. Injection device according to any one of the preceding claims 1-7, wherein the liquid to be injected is received in a single-use capsule or ampoule insertable into the container of the propulsion system which forms a unit.

10. Injection device according to claim 9, wherein the compressible substance is permanently mounted in the container.

11. Injection device according to claim 9, wherein the compressible substence is mounted in the capsule.

12. Injection device according to anyone of claims 9-11, wherein said container comprises a separable portion, such as a cap, to open the container portion and enable the ampoule or capsule to be mounted therein.

13. Injection device according to any one of the preceding claims, further comprising retaining means comprising a plug for maintaining the pressure of the compressible substance in the container prior to use by closing an orifice or a passage.

14. Propulsion system according to claim 13, wherein the plug is a mechanical plug that may be displaced to liberate said passage or orifice.

15. Propulsion system according to claim 13, wherein the plug is made of a meltable material such as paraffin or a material that may be decomposed by external solicitation, such as localised heating.

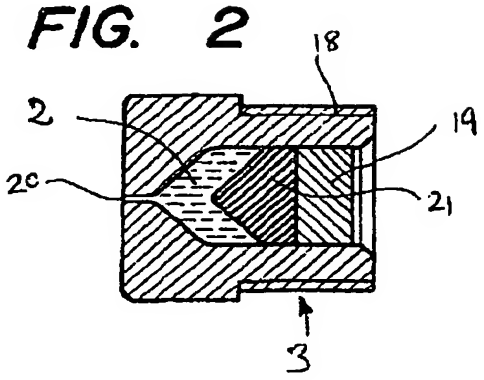
16. Device according to claim 9, wherein the ampoule comprises a flexible or deformable wall fixed to the nozzle portion to contain the fluid to be injected therein.

17. Device according to claim 16, wherein a plug is arranged in the nozzle portion.

18. Device according to claim 17, wherein the plug is made of high tensile strength wire.

B-13581 EP

FIG. 2



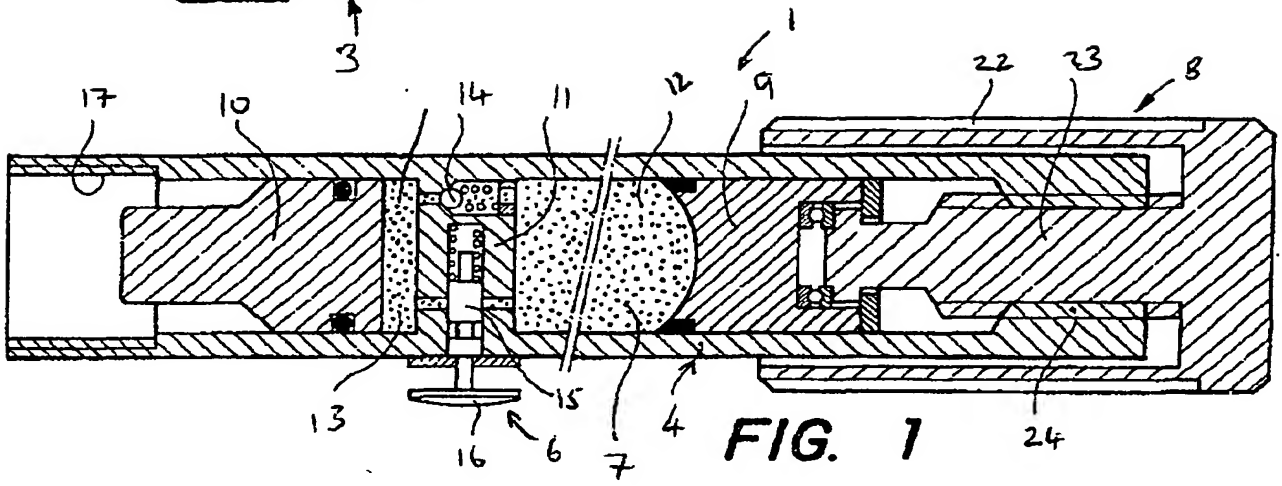


FIG. 1

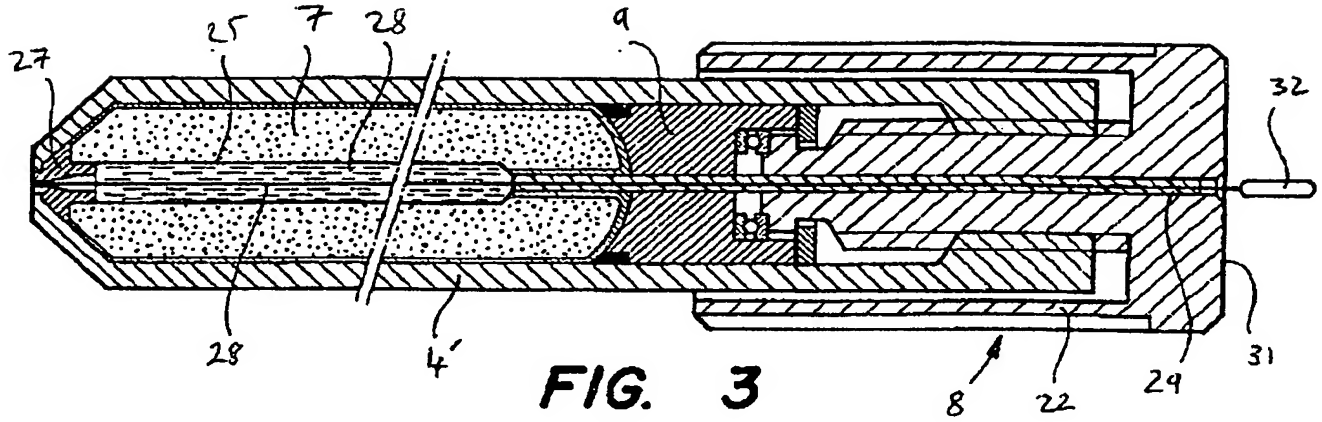


FIG. 3

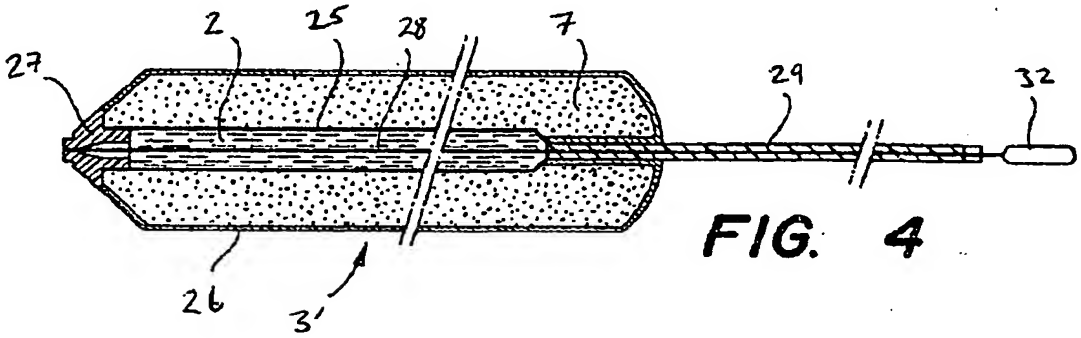
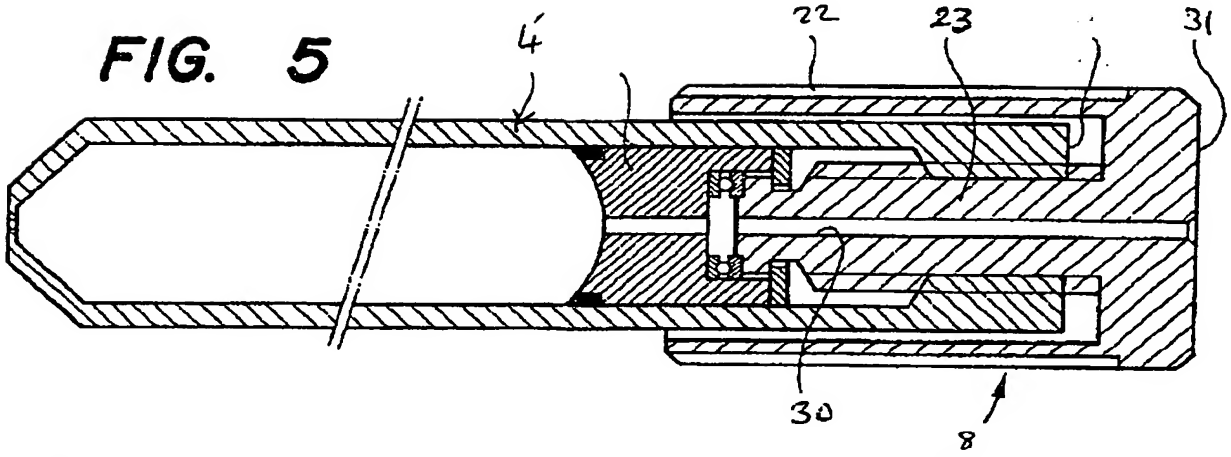


FIG. 4

FIG. 5



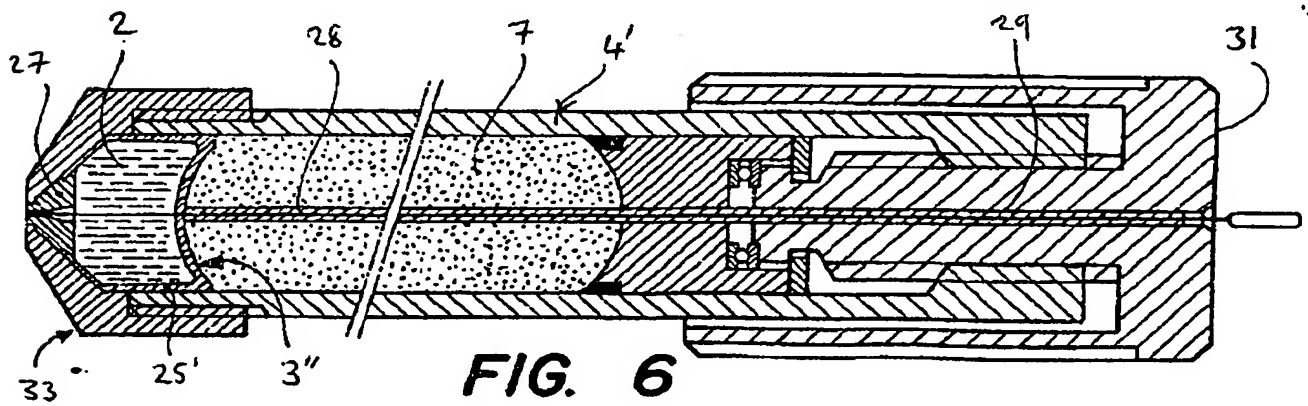


FIG. 6

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